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Epidemiology, Risk Factors and Mortality of Candidemia: Case-control Study

Kandidemi Epidemiyolojisi, Risk Faktörleri ve Mortalitesi: Olgu-kontrol Çalışması

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ABSTRACT

Introduction: *Candida species are important nosocomial bloodstream infections that cause high mortality rates and prolonged hospitalization. In this study, we aimed to determine risk factors for candidemia and the distribution of Candida species causing bloodstream infections.*

Materials and Methods: *The study was conducted as case-control study at an 810-bed tertiary care teaching hospital between April 2014 and April 2017.*

Results: *A total of 75 candidemia episodes were identified during the study period. Candida albicans was the most-frequent species (68%), followed by Candida glabrata (9.3%), and Candida tropicalis (6.7%). The rate of candidemia was higher in intensive care units than in other units. Prior antibiotic use [Odds Ratio (OR)= 15.52; 95% confidence interval (CI) 6.025-39.99; p< 0.0001], duration of hospitalization (OR= 1.043; 95% CI 1.007-1.08; p= 0.019), and total parenteral nutrition (OR= 1.181; 95% CI 1.032-1.353; p= 0.016) were found to be independent risk factors for candidemia.*

Conclusion: *A better understanding of the risk factors for candidemia among hospitalized patients may have significant implications for prevention.*

Key Words: *Candidemia; Risk factors; Bloodstream infection*

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ÖZ

Kandidemi Epidemiyolojisi, Risk Faktörleri ve Mortalitesi: Olgu-kontrol Çalışması

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Giriş: *Kandidaların etken olduğu kan dolaşımı infeksiyonları, yüksek mortalite oranları ve hastane yatış sürelerini uzatmaları açısından önemli nozokomiyal infeksiyonlar arasındadır. Bu çalışmada, üçüncü basamak sağlık hizmeti veren bir üniversite hastanesinde kandidemi risk faktörlerini ve etken olan kandida türlerinin saptanması amaçlanmıştır.*

Materyal ve Metod: *Çalışma 810 yataklı üçüncü basamak bir üniversite hastanesinde Nisan 2014-Nisan 2017 tarihleri arasında olgu-kontrol çalışması olarak yürütüldü.*

Bulgular: *Çalışma süresi boyunca toplam 75 kandidemi olgusu değerlendirilmiştir. En sık kandidemi etkeni Candida albicans (%68) olarak bulunmuştur. Candida glabrata (%9.3) ve Candida tropicalis (%6.7) diğer sık etkenler olarak tespit edilmiştir. Yoğun bakım ünitelerinde kandidemi sıklığı diğer ünitelerden daha fazla bulunmuştur. Daha önceden antibiyotik kullanımı [Odds Ratio (OR)= 15.52; %95 güven aralığı (GA) 6.025-39.99; p< 0.0001] ve total parenteral nütrisyon (OR= 1.181; %95 GA 1.032-1.353; p= 0.016) kandidemi için bağımsız risk faktörleri olarak bulunmuştur.*

Sonuç: *Kandidemi risk faktörlerinin iyi anlaşılması hastanede uzun süreli yatan hastalarda bu infeksiyonların önlenmesi için önemlidir.*

Anahtar Kelimeler: *Kandidemi; Risk faktörleri; Kan dolaşımı infeksiyonu*

INTRODUCTION

Candidemia has often been cited as the fourth most-common bloodstream infection and the third most-common cause of infections in intensive care units (ICUs)[1]. Bloodstream infections caused by *Candida* species account for 9% of hospital-acquired bloodstream infections[2]. Mortality rates are high in patients with candidemia, reaching 40-50%[3-6]. In previous studies, several factors, including the presence of indwelling catheters, the use of broad-spectrum antibiotics, total parenteral nutrition (TPN), intraabdominal surgery, and ICU admission have been shown to be possible risk factors for candidemia. In addition, studies have indicated that the epidemiology of candidemia has been shifting during recent years from *Candida albicans* species toward non-*albicans Candida*[7]. The differences in the epidemiology of candidemia can vary depending on medical practices, patient age, surgical procedures, antifungal drug use, geographical region, and even between hospitals in the same area. The knowledge of local epidemiology is helpful for choosing adequate antifungal therapy and reducing mortality[8,9].

A great number of these infections are preventable by reducing risk factors and through early diagnosis. Therefore, predicting candidemia and determining its risk factors are of paramount importance not only for treatment but also for diagnostic approach[9].

In this study, we aimed to determine risk factors for candidemia within a prospective case-control study at a university hospital.

MATERIALS and METHODS

This study was conducted between April 2014 and April 2017 as case-control study at a tertiary university hospital with an 810-bed capacity; 69 of these were ICU beds. Approval for the study was obtained from the Pamukkale University Medical Faculty Ethics Committee (08/08.04.2014). During the study period, all patients > 18 years diagnosed with candidemia were included in the patient group. Candidemia was diagnosed with the isolation of any species of *Candida* in at least one blood culture of patients who presented with clinical signs or symptoms of infection[10]. The first episode of candidemia was included in the

analysis. The control group comprised age- and sex-matched patients hospitalized in the same services as the patient group at the same time and who had no clinical or laboratory findings for bloodstream infection. Data for patients in the patient and control groups were recorded on a prepared form and based on bedside visits and patient records. In addition to demographic data, the form included data regarding diabetes, chronic renal failure, cancer, HIV infection, surgical intervention, cancer and chemotherapy, healthcare-related risk factors of infection, previous use of antibiotic therapy, central venous catheter (CVC), dialysis, mechanical ventilation, tracheostomy, urinary catheter, TPN, history and duration of hospitalization, use of antibiotics, and clinical and laboratory findings of candidemia and clinical outcomes.

Blood specimens were cultured in BACTEC blood culture system (BD, New Jersey, USA). After positive BACTEC blood culture signaling, sheep blood agar and Sabouraud dextrose agar were used for sub-culturing and incubating at 37°C. Gram stain, germ tube production, Dalmau agar microscopy, and BD Phoenix Yeast ID results from yeast-like colonies were used for identification.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corporation, USA). Comparisons of the groups for normally distributed continuous variables were made using t-test and Mann-Whitney U test for skewed continuous variables. Categorical data were analyzed using the Chi-square test or Fisher's exact test. All variables found significant for risk in the univariate analysis were incorporated into the model, and logistic regression analysis was adjusted and conducted with retrospective variable selection; $p< 0.05$ values were considered statistically significant.

RESULTS

A total of 75 patients with candidemia [36 females (48%); mean age of all patients 60.25 ± 17.17 years] were included into the study. Close to half of the patients (45.4%) were hospitalized in the ICU (Table 1).

Distribution of the patients according to the clinic of hospitalization, mean age, and sex were similar between the study and control groups. Demographic features and results of the univariate analysis for the risk factors of candidemia are shown in Table 2. In our study, mortality rate was determined as 48%.

Table 1. Distribution of candidemia cases according to the clinics

Clinic of hospitalization	n (%)
Intensive care	
Anesthesia	29 (38.7)
Neurosurgery	2 (2.7)
Coronary	2 (2.7)
Neurology	1 (1.3)
Internal medicine	
Oncology	19 (25.3)
Hematology	6 (8)
Nephrology	4 (5.3)
Gastroenterology	1 (1.3)
Rheumatology	1 (1.3)
Infectious diseases	2 (2.7)
Pulmonary diseases	2 (2.7)
General surgery*	2 (2.7)
Urology	2 (2.7)
Dermatology	1 (1.3)
Orthopedics	1 (1.3)
Total	75 (100)

* 14 patients transfer to the intensive care unit after abdominal surgery.

C. albicans was the most-frequently isolated species, followed by *Candida glabrata* (9.3%), *Candida tropicalis* (6.7%), *Candida kefyr* (5.3%), and *Candida parapsilosis* (5.3%) (Table 3).

When categorical variables were evaluated with univariate analysis, the presence of CVC ($p= 0.003$), administration of TPN ($p= 0.005$), surgical procedure within the last 30 days ($p= 0.037$), and use of antibiotics ($p< 0.0001$) were statistically higher in the patient group than in the control group. This was particularly significant in patients using beta-lactam/beta-lactamase inhibitors ($p< 0.0001$). Although not statistically significant, blood transfusion ($p= 0.050$) and hemodialysis ($p= 0.086$) rates were higher in the patient group while chemotherapy ($p= 0.061$) rates were higher in the control group. When continuous variables were compared with univariate

Table 2. Patient characteristics and risk factors of candidemia

Variables	Patient group [n= 75 (%)]	Control group [n= 75 (%)]	p
Age, year (mean ± SD)	60.25 ± 17.17	59.96 ± 15.4	0.913
Duration of hospitalisation, day, median (IQR)	16 (8-30)	6 (4-13)	0.000
Duration of hospitalisation in intensive care unit, day, median (IQR)	14 (8-32)	7 (3-14)	0.024
TPN duration, day, median (IQR)	13 (8-23)	7 (6-14.75)	0.027
Catheter duration, day, median (IQR)	23 (12-45)	7 (2.75-19.25)	0.003
Duration of antibiotics use, day, median (IQR)	10 (7-15)	7 (4.25-13.75)	0.109
Female sex	36 (48)	35 (46.7)	0.870
Diabetes mellitus	17 (22.7)	10 (13.3)	0.137
Chronic renal failure	12 (16)	6 (8)	0.132
Malignancy	38 (50.7)	29 (38.7)	0.139
Neutropenia	6 (8)	1 (1.3)	0.116
History of hospitalisation (last 6 months)	27 (36)	23 (30.7)	0.488
Hospitalisation more than two days (last 3 months)	25 (33.3)	20 (26.7)	0.373
Mechanical ventilation	30 (40)	23 (30.7)	0.232
Hemodialysis	13 (17.3)	6 (8)	0.086
Urinary catheter	39 (52.0)	32 (42.7)	0.252
Transfusion	46 (61.3)	34 (45.3)	0.050
Total parenteral nutrition	27 (36)	12 (16)	0.005
Chemotherapy	4 (5.3)	12 (16)	0.061
History of surgical intervention (last 30 day)	24 (32)	13 (17.3)	0.037
Central venous catheter	32 (42.7)	15 (20.0)	0.003
Jugular	22 (29.3)	10 (13.3)	0.017
Femoral	7 (9.3)	5 (6.7)	0.547
Port catheter	4 (5.3)	0	0.120
Use of antifungal	2 (2.7)	0	0.497
Use of antibiotic	55 (73.3)	12 (16)	0.000
Third-Fourth generation cephalosporin	6 (8)	8 (10.7)	0.575
Piperacillin-tazobactam	17 (22.7)	1 (1.3)	0.000
Carbapenem	30 (40)	3 (4)	0.000
Quinolone	2 (2.7)	0	0.497

analysis, durations of hospitalization (p< 0.0001), hospitalization in an ICU (p= 0.024), TPN (p= 0.027), and CVC (p= 0.003) were statistically longer in the patient group.

The use of antibiotics, duration of hospitalization, presence and duration of TPN, duration of hospitalization in ICUs, and history of a surgical procedure within the last 30 days, presence and duration of CVC that revealed p< 0.05 values were evaluated with multivariate analysis. The use of antibiotics in the previous 30 days (p< 0.0001; OR= 15.52; 95% CI, 6.025-39.99), the duration of hospitalization (p= 0.019; OR= 1.043; 95% CI, 1.00-1.08), and TPN duration (p= 0.016; OR= 1.181; 95% CI, 1.032-1.353) were found to be independent risk factors for candidemia (Table 4).

Table 3. *Candida* species that were isolated from blood cultures

***Candida* species**	**n= 75 (%)**
Candida albicans	51 (68)
Candida glabrata	7 (9.3)
Candida tropicalis	5 (6.7)
Candida kefyr	4 (5.3)
Candida parapsilosis	4 (5.3)
Candida dubliniensis	3 (4)
Candida lusitaniae	1 (1.3)

Table 4. Multivariate logistic regression analysis of independent risk factors of candidemia

	Adjusted ratio*	**95% confidence interval**	**p**
Duration of hospitalization	1.043	1.007-1.08	0.019
Use of antibiotics	15.52	6.025-39.99	< 0.0001
TPN duration	1.181	1.032-1.353	0.016

TPN: Total parenteral nutrition.
* Model of regression analysis was adjusted as age and sex.

DISCUSSION

Mortality rates are high in candidemia, and the incidence is gradually increasing. In the present study, we found that the mortality rate from candidemia was 48%. Similarly, a more-recent Turkish study has found a 30-day mortality rate of 41% in patients with candidemia[5]. In another study from Turkey, the rate of mortality has been reported as 83% in patients with candidemia among intensive care units[11]. Ulukilic et al. have reported a mortality rate of 36% for *C. albicans* and 39% for non-albicans[12]. Delaying or failing to initiate treatment in cases of candidemia are among the factors affecting mortality rate[13,14]. The prolonged time between taking a blood culture and beginning antifungal therapy is related to an increase in the rate of mortality[15]. Therefore, in the management of candidemia, it is important to initiate treatment empirically in the early period with an appropriate antifungal agent[13-16]. Diagnostic values of non-culture-based methods to diagnose candidemia are limited in patients with low-risk candidemia, and these methods cannot be used widely[13,17]. For these reasons, determining risk factors for candidemia remains necessary for diagnostic approach and appropriate treatment. In our study, the use of antibiotics, duration of TPN, and duration of hospitalization were determined to be independent risk factors for the development of candidemia.

In our study, candidemia was caused by *C. albicans* in 51 (68%) patients, and non-albicans *Candida* species were found in 24 (32%) patients. Although non-albicans *Candida* species have been increasingly identified as the causative agents in candidemia in several recent studies, we found a low rate of 32%. Similarly, a study from Italy has showed *C. albicans* (61.2%) as the most commonly isolated in candidemia, following *C. parapsilosis* and *C. glabrata*[9]. The studies from Turkey have reported the rate of *C. albicans* candidemia as at least 50%, but in a multicenter study, this rate has been detected as 45.8%[11,18-20]. Another multicenter study (39 facilities) has found that although the incidence of *C. albicans* candidemia was decreasing, *C. albicans* still had the most species isolated. In the same study, increased candidemia incidence with *C. parapsilosis* and *C. tropicalis* was reported[16]. We isolated the most-common non-albicans *Candida* species as *C. glabrata* and *C. tropicalis* respectively. Similarly, Chow et al. have reported that *C. glabrata* and *C. tropicalis*

were the most-common isolates in non-albicans *Candida*[21]. We posit that the limited use of prophylactic fluconazole in our hospital might be associated with a high rate of *C. albicans*.

Previous studies have also determined that the use of broad-spectrum antibiotics is a risk factor for candidemia in line with our results[20,22,23]. Candidemia rates were found to be highest in Spain and Italy, where the frequency of antibiotic use is the highest[5]. In terms of antibiotic class, the previous use of piperacillin-tazobactam and carbapenems was a risk for candidemia. Similar to our results, a study with non-neutropenic patients has found that the use of broad-spectrum antibiotics was an independent risk factor for candidemia, due especially to the common use of meropenem[24].

The duration of hospitalization was another risk factor determined by the multivariable analysis and was related to increasing the risk of candidemia 1.043 times for each day of hospitalization (p= 0.019). Kulberg likewise has shown that a duration of hospitalization longer than 20 to 25 days was a risk factor for candidemia[24]. This duration has been reported as > 9 days and > 14 days in other studies[22,23].

The duration of TPN treatment was associated with an increased risk for candidemia of 1.181 times for each day in the present study. Similarly, another study has identified TPN duration as a risk factor for candidemia[25].

Patients hospitalized in ICUs, patients who had undergone abdominal surgery, and immunosuppressed patients are at risk for candidemia[5,11,26]. In our study, candidemia patients were hospitalized mainly in the ICU, oncology, and hematology clinics. Only two patients developed candidemia when they were hospitalized in the general surgery clinic. By contrast, 14 patients developed candidemia during their transfer to the intensive care unit following abdominal surgery. Although we didn't identify a risk factor in the multivariate analysis, a history of surgical intervention within the last 30 days was found to be higher in the patient group compared to the control group in the univariate analysis (p= 0.037). In a study, most ICU patients with candidemia following surgical intervention had undergone abdominal surgery[27]. In a previous study comparing patients with candidemia in an ICU and in a surgical ward, hospitalization in the ICU has been found to have a higher risk for candidemia. This was associated with ICU patients being subjected to more invasive interventions and the use of broad-spectrum antibiotics[19,26].

This study has several limitations. Although the study was performed prospectively, colonization before candidemia could not be evaluated since routine serial cultures are not conducted at our center. As the number of non-*albicans Candida* species was small, we could not determine the risk factors according to species.

CONCLUSION

In the present study, we found *C. albicans* to be the first cause of candidemia (68%). Duration of hospitalization, use of broad-spectrum antibiotics, and TPN were independent risk factors for candidemia in this population. A better understanding of the risk factors for candidemia among hospitalized patients may have significant implications for its prevention.

ETHICS COMMITTEE APPROVAL

Approval for the study was obtained from the Pamukkale University Medical Faculty Ethics Committee (08/08.04.2014).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: SSK, CK

Analysis/Interpretation: MK, KÖ

Data Acquisition: CK, ÇE

Writting: KÖ, MK, SSK

Final Approval: All of authors

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